A STUDY OF SENTINEL LYMPH NODE BIOPSY FOR CARCINOMA BREAST

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"SENTINEL LYMPHNODE BIOPSY IN CARCINOMA BREAST"** submitted by **Dr. A. KUMARAVEL** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of **M.S Degree Branch – I (General Surgery)** is a bonafide research work were carried out by her under direct supervision & guidance.

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DECLARATION

I **Dr. A. KUMARAVEL** declare that, I carried out this work on, **"SENTINEL NODE BIOPSY IN CARCINOMA BREAST"** at the Department of Surgery, Govt. Rajaji Hospital during the period of June 2006 to October 2008. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.S degree examination in General Surgery.

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INTRODUCTION

The standard level 1 and 2 axillary lymph node dissection (ALND) has been a routine component of the surgical care of the breast cancer patients over the past century, by providing the prognostically powerful definitive proof of axillary node negative v/s positive disease historically, ALND with surgical removal of nodal metastases in level 1&2 of the axilla was thought to aid in achieving excellent local –regional control of disease in breast cancer patients the extent to which an ALND contributes to breast cancer survival, however, is uncertain. The prognostic and staging benefits of the ALND must be weighted against the acknowledged morbidity associated with the procedure. When suitable alternatives to ALND were considered, clinical examination and imaging modalities failed to consistently stage the axilla with accuracy. As a result intraoperative lymphatic mapping (IOLM)rapidly emerged as a primary approach to staging the axilla .

Sentinel lymph node biopsy (SLN) has proven to be an accurate and less morbid, minimally invasive approach to evaluating the status of axillary lymph nodes. Many institutions have come to accept a negative SLN as accurate means of identifying the node negative patients for whom the ALND can be avoided .a completion ALND remains standard care for a patient who has a positive SLN

AIMS OF STUDY

The aims of this study are to determine

1. To study the incidence of Sentinel Lymph Node Biopsy positivity for Carcinoma Breast, by using methyline blue dye in Govt. Rajaji Hospital, Madurai.
2. Investigations done and their usefulness in clinching the diagnosis.
3. The treatment offered and the outcome.

OVER VIEW OF CARCINOMA OF THE BREAST

Breast Cancer is the most common cause of death in middle aged women in Western countries. In 1998, approximately one million new cases were diagnosed worldwide. In England and Wales, one in 12 women will develop the diseases during their lifetime.

Investigation of a breast Lump (after imaging performed) Using fine – needle aspiration with cytology.

By age 25	1 in 19 608	By age 60	1 in 24
By age 30	1 in 2525	By age 65	1 in 17
By age 35	1 in 622	By age 70	1 in 04
By age 40	1 in 217	By age 75	1 in 11
By age 45	1 in 93	By age 80	1 in 10
By age 50	1 in 50	By age 85	1 in 9
By age 55	1 in 33	Ever	1 in 8

Aetiological factors:

Geographical :

It occurs commonly in the Western World, accounting for 3-5% of deaths, yet is rare tumour in Japan. In developing countries, it accounts for 1 to 3 % of deaths.

Age

Carcinoma of the breast is extremely rare below the age of 20 years but, thereafter, the incidence steadily rises so that by the age of 90 years nearly 20% of women are affected.

Gender

Less than 0.5% of patients with breast cancer are male.

Genetic

It occurs more commonly in women with a family history of breast cancer than in the general population. Breast cancer related to a specific mutation accounts for about 5% of breast cancers, yet has far reaching repercussions in terms of counseling and attempted prevention in these women.

Breast cancer syndrome

1. Li-Fraumeni syndrome

   P53 gene mutation

   Autosomal dominant mutation

2. Cowden's disease

   Multiple hamartoma syndrome

   Facial trichilemmoma, papilloma, bilateral breast cancer

3. Ataxia telangiectasia

   Hemangioma breast cancer

Chromosomal Abnormalities

1. BRCA one gene mutation – Chromosome 17q

   Poorly differentiated

   Invasive ductal type

   Hormone receptor negative

   Associated with ovarian, prostate and colon cancers

2. **BRCA-2 gene mutation – Chromosome 13 q**

Well differentiated

Invasive ductal carcinomas

Express hormone receptors

Associated with ovarian, colon, prostate, pancreas, gallbladder, bile duct, stomach cancers and melanoma

3. HER-2 mutation (rbB2, transmembrane growth factor)

Invasive breast cancer ; upto 80% ductal carcinoma

Poor diagnosis

4. P 53 mutation

Associated with poor diagnosis

Resistance to chemotherapy

Diet

Because breast cancer so commonly affects women in the developed world, dietary factors may play a part in its causation. There is some evidence that there is a link between diets low in phyto-oestrogens. A high intake of alcohol is associated with an increased risk of developing breast cancer.

Endocrine.

Breast cancer is commoner in nulliparous women and breast feeding in particular appears to be protective. Also protective is having a first child at an early age, especially if associated with late menarche and early menopause. It is known that in post menopausal women, breast cancer is more common in the obese. This is thought to be because of an increased conversion of steroid hormones to oestradiol in the body fat. The role of exogenous hormones, in particular the oral contraceptive pill and HRT, i9n the development of breast cancer is more controversial, but it can be said with some authority that for most women the benefits of these treatments will far outweigh the small putative risk.

Risk of developing breast cancer

The increase in the likelihood of developing breast cancer associated with the above risk factors

is usually quantified in terms of the relative risk (RR). Thus, an RR of 2.0 means that the individual has twice the chance of developing breast cancer as the average for the population, whereas an RR of 0.5 indicates a risk reduction of 50%.

Pathology

Breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of major lactiferous ducts to the terminal duct unit, which is in the breast lobule. The disease may be entirely in situ, an increasingly common phenomenon with the advent of breast cancer screening, or may be invasive cancer. The degree of differentiation of the tumour is usually described by three grades: well differentiated, moderately differentiated or poorly differentiated. Commonly, a numerical grading system based on the scoring of three individual factors (nuclear pleomorphism, tubule formation and mitotic rate) is used. With grade III cancers roughly equating to the poorly differentiated group.

Previously, descriptive terms were used to classify breast cancer (scirrhous, meaning woody, or medullary, meaning brain like). More recently, histological descriptions have been used. These have been shown to have clinical correlations in the way the tumour behaves and are likely to be used for the near future. However, with the increasing application of molecular markers, there will be a change and it is likely that much more information about an individual tumour will be routinely reported, such as its likelihood of metastasis and to which therapeutic agents it will be susceptible.

Current nomenclature

Ductal carcinoma is the most common variant, but lobular carcinoma occurs in up to 15% of cases. There are subtypes of lobular cancer including the classical type, which carries a better prognosis than the pleomorphic type. Occasionally, the picture may be mixed with both ductal and lobular features. Rarer histological variants, usually carrying a better prognosis, included colloid

carcinoma, whose cells produce abundant mucin, medullary carcinoma with solid sheets of large cells often associated with a marked lymphocytic reaction and tubular carcinoma. Invasive lobular carcinoma is commonly multifocal and/or bilateral. Cases detected via the screening programme are often smaller, better differentiated and of special type than those presenting to the symptomatic service.

Inflammatory carcinoma is a fortunately rare, highly aggressive cancer that presents as a painful, swollen breast, which is warm with cutaneous oedema. This is due to blockage of the subdermal lymphatics with carcinoma cells. Inflammatory cancer usually involves at least one-third of the breast and may mimic a breast abscess. A biopsy will confirm the diagnosis and show undifferentiated carcinoma cells. Its used to be rapidly fatal with surgery only hastening the end nut, with aggressive chemotherapy and radiotherapy with salvage, surgery, the prognosis has improved considerably.

In situ carcinoma is preinvasive cancer that has not breached the epithelial basement membrane. This was previously a rare, usually asymptomatic finding in breast biopsy specimens, but is becoming increasingly common owing to the advent of mammographic screening: it now accounts for over 20% of cancers detected by screening in the UK. In situ carcinoma may be ductal (DCIS) or lobular (LCIS), the latter often multifocal and bilateral. Both are markers for the later development of invasive cancer, which will go on to develop in at least 20% of cases. Although mastectomy is curative, this is over treatment in many cases and the best treatment for in situ carcinoma is the subject of a number of clinical trials. DCIS may be classified by the Van Nuys system, which combines the patient's age, type of DCIS and presence of microcalcification, extent of resection margin and size of diseases. Patients with a high score benefit from radiotherapy after excision, whereas those of low grade, who are completely excised, need no further treatment.

Staining for oestrogen and progesterone receptor (ER and PR) is now considered routine, as their presence will indicate the use of adjuvant hormonal therapy with tamoxifen. Increasingly, tumours are stained for C-erbB2 (a growth factor receptor), as patients can be treated with the

monoclonal antibody against this receptor if they relapse.

The pathologist is an important member of the breast cancer team and will increasingly help decide which adjuvant therapies will be appropriate.

Paget's disease of the nipple

Paget's disease of the nipple (Fig.55.27a. and b.) is a superficial manifestation of an underlying breast carcinoma. It presents as an eczema-like condition of the nipple and areola, which persists despite local treatment. The nipple is eroded slowly and eventually disappear. If left, the underlying carcinoma will sooner or later become clinically evident. Nipple eczema should be biopsed if there is any doubt about its cause. Microscopically, Paget's diseases is characterized by the presence of large, ovoid cells with abundant, clear, pale-staining cytoplasm in the Malpighian layer of the epidermis.

THE SPREAD OF BREAST CANCER.

Local spread

The tumour increases in size and invades other portions of the breast. It tends to involve the skin and to penetrate the pectoral muscles and even the chest wall.

Lymphatic metastasis

Lymphatic metastasis occurs primarily to the axillary lymph nodded and to the internal mammary chain of lymph nodes. The site of the tumour within the breast does not dictate which nodes will be involved, for example medial tumours spread just as readily to the axillary nodes as do lateral tumours. The involvement of lymph nodes is not just a chronological event in the evolution of the carcinoma, bit rather a marker for the metastasis potential of the tumour. Involvement of supraclavicular nodes and of any contralateral lymph nodes represents advanced disease.

Spread by the bloodstream.

It is by this route that skeletal metastases occur, although the initial spread may be via the lymphatic system. In order of frequency, the lumbar vertebrae, femur, thoracic vertebrae, rib and skull

are affected and these deposits are generally osteolytic. Metastases any also commonly occur in the liver, lung and brain and occasionally, the adrenal glands and ovaries, but have been described in most body sites.

Clinical presentation

Although any portion of the breast, including the axillary tail, may be involved, breast cancer is found most frequently in the upper, outer quadrant. Most breast cancers will present as a hard lump, which may be associated with in drawing of the nipple. As the disease advances locally there may be skin involvement with peau d'orange or frank ulceration and fixation to the chest wall. This is described as cancer-en-cuirasse. About 5% of breast cancers in the UK will present with either locally advanced disease or symptoms of metastatic disease. This figure is nearer 20% in the developing world. These patients must then undergo a staging evaluation so that the full extent of their disease can be ascertained. This will include a careful clinical examination, chest radiograph, serum alkaline phosphatase and gamma-glutamine transaminase (GGT), with liver ultrasound if these are abnormal and an isotope bone scan. This is important for both prognosis and treatment: a patient with widespread visceral metastases may obtain an increased length and quality of survival from systemic hormone or chemotherapy, but she is not likely to benefit from surgery as she will die from her metastases before local disease become becomes a problem. In contrast, patients with relatively small (less than 5cm in diameter) tumours confined to the breast and ipsilateral lymph nodes rarely need staging beyond a good clinical examination as the pick-up rate for distant metastases is so low. Currently, a chest radiograph, full blood count and liver function tests are all that are recommended for screening for patients with early-stage breast cancer. Phenomena resulting from lymphatic obstruction in advanced breast cancer.

Peau d'orange

Peau d'orange is due to cutaneous lymphatic oedema. Where the infiltrated skin is tethered by

the sweat ducts, it cann0t swell, leading to an appearance like orange skin. Occasionally the same phenomenon is seen over a chronic abscess.

Late oedema of the arm is a troublesome complication of breast cancer treatment, fortunately seen less often now that radical axillary dissection and radiotherapy are rarely combined. However, it does still occur occasionally after either modality of treatment alone and appears at any time from months to years after treatment. There is usually no precipitating cause but recurrent tumour should be excluded as neoplastic infiltration of the axilla can cause arm swelling due to both lymphatic and venous blockage. This neoplastic infiltration is often painful due to brachial plexus nerve involvement.

An oedematous limb is susceptible to bacterial infections following quite minor trauma and these require vigorous antibiotic treatment. Antibiotics may need to be given for much longer than is normal and patients at risk of infection should have antibiotics readily available in order to start treatment promptly. Treatment of late oedema is difficult but limb elevation, elastic arm stockings and pneumatic compression devices can be useful.

Cancer-en-cuirasse.

The skin of the chest is infiltrated with carcinoma and has been likened to a coat. It may be associated with a grossly swollen arm. This usually occurs in cases with local recurrence after mastectomy, and occasionally is seen to follow the distribution of irradiation to the chest wall. The condition may respond to palliative systemic treatment, but prognosis in terms of survival is poor.

Lymphangiosarcoma

Lymphangiosarcoma is a rare complication of lymphoedema with an onset many years following the original treatment. It takes the form of multiple subcutaneous nodules in the upper limb and must be distinguished from recurrent carcinoma of the breast. The prognosis is poor but some cases respond to cytotoxic therapy or irradiation. Interscapulothoracic forequarter amputation is sometimes indicated.

Staging of breast cancer

There are two traditional systems of classification for breast carcinoma, which predominantly rely on clinical staging of the disease. These are the Manchester system and the International Union Against Cancer TNM (tumour, nodes, metastases)staging system.

Stage	Tumour grade	Clinical extent	Node grade	Clinical extent	Distant metastases
TIS	TIS	No palpable tumour	N0	No nodal metastases	M0 = No known distant metastases
I	T1	<2 cm	N0	No nodal metastases	
II	T2	2-5 cm	N1	Mobile axillary nodes	
IIIa	T3	>5 cm	N2	Fixed axillary nodes	
IIIb	T4	Any size invading skin & or chest wall	N3	Supraclavicular ipsilateral nodes	
IV	Any T		Any N		M1= distant metastases

The TNM system was an attempt to allow a common language among oncologists worldwide, thus allowing accurate information exchange and evaluation of studies of treatment, as well as providing prognostic information to aid in the planning of treatment for the individual patient. However, this refinement of taxonomy in fact contributes little to any of these activities.

Further subdivisions in the TNM system now mean that there are seven T-Stages, four N-stages and three M-stages, allowing for 180 possible combinations. Pathological lymph node staging depends on both the number of lymph nodes removed, thus the extend of surgery, and how assiduous the pathologist is in looking for deposits of tumour within thee nodes. ‘M’ staging depends on what investigation have been performed, thus will vary between centres. Consequently staging is observer biased.

Although prognosis broadly correlates with stage, other factors also influence prognosis and should be assessed, for example the Nottingham Prognostic Index includes not only tumour size and lymph node status but also tumour grade. This has been validated in many centres and consists of a score given by the formulae I= (0.2x size) + grade + nodes. The size is in centimeters, the grade is on a 1-3 score and the nodes are also scored on 1-3 where a score of one indicates no nodal involvement, two indicates on e the there nodes involved. Based on the overall index, patients can be divided into an excellent prognosis group, a moderate prognosis group and a poor prognosis group. The chance of dying from breast cancer in the first group is so low that many patients do not require additional treatment.

Conventional staging will indicate broadly which treatment is required but again other factors may be equally important. For example, surgical treatment of a small stage I or II (T1or T2) breast tumour usually requires only wide local excision rather than mastectomy, but the latter may have to be performed if the breast is very small, the tumour central or multifocal, or for patient preference. Equally, the use of adjuvant systemic therapy is decided not only on tumour size and lymph node status but also biological measures such as oestrogen receptor status, patient age and menopausa status. Tamoxifen can be recommended irrespective of clinicopathological variable if the patient is hormone receptor positive.

Thus, as we gain more knowledge of the biological variables that affect prognosis, it becomes increasingly clear that it is these factors (discussed in more details below), rather than anatomical mapping, which influence outcome and treatment. Perhaps a more pragmatic approach would be to classify patients according to the treatment that they require.

Pragmatic classification for breast cancer

Group	**Approximate 5–year survival**	**Example**	**Treatment**
‘very-low-risk primary breast cancer	>90%	Screen-detected DCIS, tubular or special types	Local

'Low-risk primary breast cancer	70-90%	Node negative with favourable histology	Locoregional with/ without systemic
'High-risk primary breast cancer	<70%	Node positive with unfavourable histology	Locoregional with systemic
Locally advanced	<30%	Large primary or inflammatory	Primary systemic
Metastatic	-	-	Primary systemic

Prognosis of breast cancer

The best indicators of likely prognosis in breast cancer are still tumour size and lymph node status. However, it is realised that some large tumours will remain confined to the breast for decades, whereas some very small tumours are incurable at diagnosis. Hence the prognosis of a cancer depends not on tis chronological age but on its invasive and metastatic potential. In an attempt do define which tumours will behave aggressively, and thus require early systemic treatment, a host of prognostic factors has been described. These include histological grade of the tumour, hormone receptor status, measures of tumour proliferation such as S-phase fraction and thymidine labeling index, growth factor analysis and oncogene or oncogene product measurements. Many other are under investigation but have proved of little practical value in patient management.

Sentinel lymphnode Biopsy :

Sentinel lymphnode biopsy, or sentinel lymph node dissection (SLND), was adapted to breast cancer in the early 1990s after the successful application of similar technique to melonama. Vital dye and / or radio labeled colloid is injected into the parenchyma immediately surrounding a primary breast cancer or in a subareolar manner. The mapping agent is then used to follow the path of lymphatic drainage to sentinel lymphnodes (SLNs), the first nodes encounter by tumour cells as the metastasize to the axilla. The pathologic status of axillary sentinel lymphnode is therefore, representative of the entire axillary basin, with tumour negative SLNs predicting that nonsentinel nodes will also be tumour free. On the other hand, tumour positive SLNs indicate possible metastasis to nonsentinel nodes in the same

drainage basin and usually warrant additional surgical interventions.

Although axillary lymphnode dissection (ALND) is highly accurate, it carries a risk of significant complications. SLND is much less invasive than ALND but provides the same staging information with more accuracy and less morbidity. Numerous studies have demonstrated the accuracy of SLND in breast cancer, with SLN idenfication rates of 95% or higher and false negative rates of less than 5%.

Indication for SLND :

Early invasive breast cancer who presents without clinically palpable axillary nodes, including patients who have undergone previous excisional biopsy.

Two mapping agents :

1. (a) Vital blue dye (Isosulfan) (b) Metheline blue

2. Technetium labeled sulphor colloid use with gamma probe

Site of Injection :

Peritumoral, subareolar, combined

LITERATURE REVIEW OF SENTINEL NODE BIOPSY

The axillary nodal status is accepted universally as the most powerful prognostic tool available for early stage breast cancer. Breast cancer patients routinely undergo surgical staging of the axilla because other primary tumor features are inadequate in predicting the presence versus absence of nodal positivity. The status of the axillary lymph nodes also guides treatment options and adjuvant therapies. The removal of level I and level II lymph nodes at axillary node dissection (ALND) is the most accurate method to assess nodal status, and it is the universal standard. ALND is associated with several adverse long-term sequelae including lymphedema, the disruption of nerves in the axilla, chronic shoulder pain, weakness, and joint dysfunction. Additionally, the survival advantage of ALND has been challenged, and less morbid methods of evaluating the axillary nodal basin have been sought.

Breast cancer spreads from the tumor bed to one or a few lymph nodes before it spreads to other axillary nodes. These sentinel nodes can be identified and surgically excised for histological analysis. Lymphatic mapping with sentinel lymph node biopsy (SLNB) has emerged as an effective method of detecting axillary metastases. Veronesi and colleagues randomly assigned 516 women with early stage breast cancer to either SLNB and ALND or SLNB alone (ALND) was performed only for axillary metastases in the SLNB-alone arm). The authors demonstrated that SLNB was accurate and reliable with false-negative rate of 80%. There Was Less Pain and better arm mobility in those who underwent SLNB only. Additionally, there were no differences in local recurrence or survical at follow-up. The NSABP-32 trial is the largest multicenter trial to date examining the safety and accuracy of SLNB. The trial randomly assigned women with clinically negative axilla to receive SLNB with an ALND or SLNB alone. Early results have demonstrated that SLNB is safe and reliable, with false-negative rates of 8% to 10%, and lower morbidity that ALND. Although the long term results are forthcoming, the clinical advantages of SLNB are apparent, and the procedure is becoming the preferred standard by patients and breast cancer surgeons.

Given the rapid growth of lymphatic mapping and SLNB, surgical groups have developed several variations in practice, and many technical aspects of the procedure are evolving. These variations have included the choice of mapping label. Radioisotope quantity and processing, label injection site, timing of radioisotope injection, and the use of preoperative lymphoscintigraphy scanning. Because these controversies have not been studied extensively in clinical trials. The method of lymphatic mapping ultimately should be selected based on those method that have been proven safe, and on the services and resources of a given breast care program.

Radioisotope alone

Krag and colleagues first described the use of radioisotope alone for breast cancer in 1993, using technetium-99m sulfur colloid and a hand-held gamma probe. The sentinel node identification rate was 98%, with a false-negative rate of 11%. Technetium-99m sulfur colloid is the most widely used radioisotope for lymphatic mapping in the United States. In Europe, technetium 99m-colloidal albumin is used most. The specific radioisotope selected for the mapping process is determined largely by availability and by the center's nuclear medicine practices. The doses of radioactive technetium vary by institution and range from 0.1 to 4mCi.

Blue dye

Isosulfan blue dye (Lymphazurin 1%, US Surgical Corp, Norwalk, CT) initially was studied extensively in lymphatic mapping for melanoma. The use of isosulfan blue dye as a single agent in SLNB for breast cancer initially was reported by Giuliano and colleagues, with sentinel node identification rates of 98%, without false-negative nodes. The major disadvantage of isosulfan blue dye is the risk of life-threatening allergic and anaphylactic reactions. The reported allergic reaction rate ranges from 1% to 3%. Most reactions consist of urticaria, rash, blue hives, and pruritus. Although rare, anaphylaxis and hypotension also have been reported. Overall, isosulfan blue dye has excellent results for lymphatic mapping in breast cancer, and is the blue dye most commonly used.

Methylene blue also has been successful in SLNB for breast cancer. Simmons and colleagues

identified the sentinel node in approximately 93% of patients studied in a cohort of more than 100 patients. Concordance with radioisotope was observed in 95%.

Additionally, methylene blue was compared with Isosulfan blue dye by blessing and colleagues in 2002. The authors found that all patients had high concomitant isotope mapping and similar sentinel node identification rates. Methylene blue is preferred by some authors because of its lower costs, and also because of its lower risk of allergic reactions. Methylene blue must be injected in the subcutaneous tissues: inadvertent injection into the dermis has resulted in severe skin reactions including necrosis and dermolysis.

Combination of blue dye and radioisotope

Several authors have demonstrated that the combination of radioisotope and blue dye for lymphatic mapping improves the sentinel lymph node (SLN) identification rate. Albertini and colleagues first reported the successful use of lymphatic mapping with both blue dye and radioisotopes prospectively. The results have been confirmed with several studies demonstrating that the combination method improves the sentinel node identification rate, and dual-agent lymphatic mapping has been accepted universally. Some centers have elected to rely on radioisotope mapping alone, given the potentially life-threatening allergic reactions of isosulfan blue dye.

Filtered versus unfiltered radioisotope

Identification of a radioactive lymph node depends upon adequate uptake of the radioisotope from the breast parenchyma by intramammary lymphatics. The radioisotope must travel from the breast to the sentinel node in a timely fashion. Radioisotope uptake and travel times ultimately depend on the size of the labeled carrier and on the amount of carrier fluid used. Large particles may not migrate to regional nodes at all (those greater than 400nm) and those too small may migrate too quickly to the entire nodal basin making identification of single sentinel nodes difficult. The size of technetium-99 sulfur colloid may be altered by the selective use of filters and the pore size of filters used. Filtration through 100 or 220 nm filters has been studied, with goals of particle size ranging from

50 to 200 nm. Filtered preparations resulting in smaller particles travel more quickly and may potentially reach more SLNs including the higher echelon nodes, if there is a prolonged interval between injection of radioisotope and surgery. The unfiltered colloid may be less likely to travel to higher echelon nodes, given its larger size and slower transit time. Linehan and colleagues compared the success of SLNB using filtered versus unfiltered technetium-99m sulfur colloid combined with blue dye mapping. Although the authors found no difference in the overall SLN identification rate, there were significantly more SLNs that were radioactive in the unfiltered group versus the filtered group (88% versus 73%; P=.03). These results suggest that filtered smaller particles may pass too quickly from the injection site through the nodal basin before the sentinel nodes are removed.

There has been no consensus on the use of filtered versus unfiltered radioisotopes for lymphatic mapping in breast cancer. The various features may be considered advantages or disadvantages, and selection depends upon the timing of surgery in relation to injection times.

Injection site for mapping agents

Peri-tumoral injection

In efforts to replicate the intramammary lymphatic pathways that may have been traversed by metastases, the initial data regarding SLNB used peri-tumoral injections of the mapping agents. For patients who have nonpalpable tumors, this method has proven difficult and time-consuming, because it requires the use of additional imaging modalities to guide the peri-tumoral injection of radioisotopes. Peri-tumoral injections also have a higher potential for shine through, where residual radioactivity from the peri-tumoral injection site creates misleading background activity detected by the gamma probe from the axilla. It is for these reasons that alternate injection sites have been pursued.

Subareolar and dermal injection

Mammary lymphatics develop as radial extensions from the nipple breast bud. Nearly all breast tissue lymphatic drainage passes through the subareolar plexus of Sappey and then into the axillary nodal basin; hence dermal and subareolar injections are potential approaches for the injection of

mapping agents. The sites are particularly advantageous for patients who have non-palpable or multicentric tumors; they also eliminate the shine through effect.

A potential disadvantage to subareolar and dermal injections is that up to 10% of breast cancer may demonstrate nonaxillary lymphatic drainage with sentinel nodes found in the internal mammary or supraclavicular nodal basins; hence not all breast tumors will have the same drainage patterns as the overlying skin and nipple areas. Additionally, subareolar and dermal injection of blue dye may cause considerable postoperative discoloration of the breast (blue breast), which may last for several months.

Veronesi and colleagues first described subdermal injections of technetium -99m labeled albumin into the dermis overlying the tumor of 163 patients undergoing SLNB and ALND. The authors found that the SLN identification rate was 98% with a false-negative rate of 4.7%. Several authors have confirmed the reliability of dermal injections by direct comparisons between peri-tumoral and skin radioisotope injections. Borgstein and colleagues studied 33 breast cancer patients undergoing lymphatic mapping, consisting of dermal injections of blue dye and peri-tumoral injections of radioisotope. The authors found 100% concordance between blue and radioactive SLNs in 30 of the 33 patients studied, without any false negatives. Linehand and colleagues studied 200 patients undergoing SLNB with peri-tumoral or excisional biopsy site blue dye injections. In the study, half of the patients also received Tc99-sulfur colloid injected peri-tumorally, and the other half received radioisotopes by means of dermal injections. The SLN identification rates were 92% for those patients receiving intraparenchymal injections of both blue dye and radioisotopes. For those patients receiving intraparenchymal injection of blue dye and dermal injection of radioisotopes, the SLN identification rate was 100%. In both subsets of patients, the concordance between blue-stained and radioactive sentinel nodes was also high (97% and 95%, respectively). Those patients receiving dermal injections of radioisotopes had a greater proportion of sentinel nodes radioactive when compared with the group receiving peri-tumoral injection of radioisotopes (97% versus 78%; $P<.001$). A subsequent report compared 134 patient receiving intraparenchymal lymphatic mapping with 164 patients with mapping

using intraparenchymal blue dye and dermal injection of radioisotopes. The SLN identification rate was significantly higher in the group receiving dermal injections of radioisotopes (98% versus 89%). There was no difference in the false-negative rates (4.4% and 4.8)

Several authors have studied the differences between lymphatic drainage pathways of intradermal versus intraparenchymal injections of radioisotopes. Shen and colleagues studied the preoperative lymphoscintigraphy scans of 30 patients undergoing lymphatic mapping for cutaneous breast melanomas and 97 patients undergoing lymphatic mapping with peri-tumoral injection for breast cancer. The authors found that there were a higher percentage of nonaxillary SLNs in the melanoma/dermal injection group (26% versus 5%). In the melanoma cases, there were bilateral axillary and supraclavicular drainage sites detected, whereas the breast cancer cases mapped to the ipsilateral axillae. The results demonstrated that axillary drainage patterns varied between peri-tumoral and dermal lymphatics. Additionally, given the importance of the ipsilateral axillary, mammary, and supraclavicular nodal basins in the staging of breast cancer, if drainage to these sites can be detected with dermal injection, the dermal route may be adequate for the staging of breast cancer.

Klimberg and colleagues compared lymphatic mapping using subareolar injections of radioisotope to peri-tumorally injected blue dye. The authors found successful mapping in 64 of 68 patients studied (94%). The SLN identification rate for blue dye was 89.9% versus an identification rate of 94.2% for radioisotope. In the study, all blue nodes were also radioactive, indicating that subareolar injection did not miss any axillary SLNs using this method of mapping.

Subareolar and dermal injection sites also have been examined using various areas of the breast for injection. Beitsch and colleagues studied subareolar radioisotope injected into the mirror-image quadrant of the nipple-areolar tissue and peri-tumoral blue dye injections. The SLN identification for blue dye and radioisotopes were 94% and 99%, respectively, and 99% of the blue SLNs were also radioactive. Kern reported successful results of lymphatic mapping using subareolar injections of blue dye and radioisotopes at the upper, outer aspect of the nipple-areolar tissue.

Although SLNB has proven reliable in women who have unifocal disease, the studies examining the ideal injection site have set the stage for the consideration of SLNB in multicentric and multifocal disease. Tousimis and colleagues reported results from the largest series examining lymphatic mapping in multicentric and multifocal breast cancer. The authors examined 70 patients who underwent mapping using a combination of radioisotopes and blue dye. In the study, 63 patients received a single intradermal injection of radioisotopes directly over the largest tumor, and five patients received radioisotope peri-tumoral radioisotope injections. Additionally, 67 patients received a single intraparenchymal blue dye injection adjacent to the supero-lateral side of the largest invasive tumor or biopsy cavity. The authors found that the accuracy (SLN identification rate of 96%) and false-negative rate (8%) of SLNB in patients who had multicentric and multifocal breast cancers were comparable to those with unifocal tumors. Though confirmatory studies are warranted, these results demonstrate the feasibility of SLNB in patients who have multicentric and multifocal breast cancer.

Preoperative Lymphoscintigraphy

Patients undergoing lymphatic mapping with radioisotopes most often receive a preoperative lymphoscintigram (PL) to aid in SLN identification. PL typically consists of anterior and lateral views and specific patient positioning to optimize transit time and radioisotope drainage. Scanning routinely is initiated 20 minutes after radioisotope injection, and images are repeated until the primary SLN basin is identified and there is adequate uptake. The patient then is taken to the operating room for SLNB.

It is controversial whether preoperative scanning is of diagnostic value. Many authors have examined the accuracy of the PL, and given the additional time and cost, question its value in improving the identification of sentinel lymph nodes. Proponents of the technique have argued that the scan may guide the timing of surgery when radioisotope injection is performed on the same day as the operation. Additionally, PL with identify the primary drainage pattern, and also internal mammary (IM) sentinel nodes. There is no consensus regarding the management IM SLNs that have been identified by PL, and current recommendations for adjuvant therapies have been defined mostly by

axillary nodal metastases. McMasters and Colleagues evaluated the role of PL in breast cancer. In the study, a PL was performed in 348 of 588 patients (59%), and 240 patients did not receive scans. The SLN was identified in 221 of the 240 (92%) patients who did not undergo preoperative scanning. In these patients, the false-negative rate was 1.6%. In those patients receiving a preoperative lymphoscintigram. The SLN was identified in 310 of the 348 (89.1%) patients, with a false-negative rate of 8.7%. The authors found no significant difference in the SLN identification rate, false-negative rate, or number of SLNs removed between patients receiving PL and those proceeding to operation without scanning. Borgstein and colleagues also studied the role of PL in breast cancer patients. The authors found that the intraoperative gamma probe was more sensitive in detecting radioactive nodes in the axilla than the PL, even when delayed images were obtained. In the study, axillary accumulation was absent in 14 of 130 patients receiving PL. The intraoperative gamma probe was unsuccessful in detecting radioactivity in 8 of 130 cases (seven of these patients also had negative PL).

Data have continued to emerge questioning the ability of PL to improve the accuracy of SLNB, and some centers have abandoned the technique, focusing only on resecting SLNs in the axilla, and relying on the intraoperative gamma probe to detect radioactive SLNs. Until there are definitive data regarding the treatment and importance of nonaxillary drainage, the decision to use PL is ultimately the decision of the surgeon and the multidisciplinary breast team.

Timing of radioisotope injection

Lymphatic mapping with radioisotopes is performed either as a 1-or 2- day procedure. The half-life of technitium-99 is approximately 6 hours and must be taken into account when planning SLNB.

The single –day procedure requires breast injection on the morning of surgery, followed by serial imaging at 1 to several hours after injection until the SLN is identified. In some cases, the process can take several hours and may significantly delay the operation. The effect of delay on patients and on operating room scheduling has led some centers to use a 2-day mapping procedure, with injection of

radioisotopes 1 day before operation. The 2-day procedure has been criticized because of the concern that it may require higher doses of radioisotopes or that with prolonged exposure, radioisotopes may move into higher-echelon nonsentinel lymph nodes. Winchester and colleagues evaluated lymphatic mapping with radioisotope injection 1 day before operation. The study consisted of 180 patients receiving lymphatic mapping and SLNB, with technitium-99 sulfur colloid injected 1 day preoperatively. The authors found that the SLN identification rate was 90%, and was influenced largely by the surgeon's learning curve. Additionally, mapping was improved when 1.0 mCi-filtered radioisotope was used (versus 0.5 to 1.0 mCi unfiltered radioisotope). McCarter and colleagues also had successful outcomes using the 2-day procedure. The authors studied 933 patients who received 0.1 mCi of dermal technitium-99 sulfur colloid in 0.05 cc normal saline on the day of surgery, and 387 patients who received 0.5 mCi technitium-99 sulfur colloid dermal injections on the day before operation. All of the patients had peri-tumoral blue dye injections intraoperatively. The median number of SLNs identified in he of isotope counts was similar between the two groups. Likewise, Solorzano and colleagues reported success with the 2-day lymphatic mapping technique. The authors found that injection of 2.5 mCi technetium sulfur colloid (filtered) peri-tumorally on the day before surgery with lymphoscintigraphy to track drainage resulted in an overall SLN identification of 97.5%. All positive SLNs with blue dye staining were also radioactive. Based on the current literature, a 2-day lymphatic mapping procedure is safe and reliable for SLNB in breast cancer.

Should axillary dissection remain the standard of care in patients with positive sentinel lymph nodes?

Morbidity associated with axillary lymph node dissection

ALND has been associated with a significant risk of lymphedema, sensory disturbances, shoulder dysfunction, wound infection, and incisional pain. ALND patients face a lifelong risk of lymphedema that ranges from 10% to 50% depending on other risk factors, duration of follow-up and method of detection. Recent data from two very large multicenter trials provide initial reports on the

morbidity associated with SLN biopsy as opposed to ALND. Among all examined variables, patients undergoing SLN biopsy fair better than patients undergoing completed axillary evaluation.

Nonsentinel node metastases

With improvements in breast cancer screening and increased public awareness, an earlier stage distribution for breast cancer and a lower incidence of axillary metastases are starting to be seen. Recent estimates suggest that only 30% of patients have evidence of axillary metastases at the time of diagnosis. Studies of patients undergoing SLN biopsy with a concomitant ALND have demonstrated that axillary metastases will be limited to the SLN in 30% to 67% of cases. Several other authors have confirmed that roughly 50% of patients who have positive SLNs subsequently are found to have no evidence of further axillary disease. Removal of negative nodes does not provide any significant benefit, yet a fair number of patients with metastases isolated to the SLN still will be subjected to ALND and all of its associated morbidity to have definitive proof of their node-negative status. There is clearly no benefit to removing negative axillary nodes, and when residual metastases do extend beyond the SLN, chemotherapy has been shown to sterilize 23% of axillary metastases.

From 1995 to 1999, Calhoun and Colleagues identified 634 breast cancer patients who underwent SLN biopsy. SLNs were scrutinized further using immunohistochemistry if hematoxylin and eosin evaluation was negative, and ALND was recommended for patients who had SLN biopsies positive by immunohistochemistry (IHC). Seventy-eight patients (12.3%) with IHC-positive SLNs were offered ALND. Sixty-one consented, whereas 17 refused. Fifty-eight (95.1%) had negative non-SLNs. Three (4.9%) had non-SLN metastases: one (1.6%) had macrometastatic disease, whereas two (3.3%) had micrometastases. Among patients with SLNs positive by IHC only, there were no axillary recurrences after a mean of 80.5 months. When ALND was performed in the setting of an IHC-positives SLN, 1.6% of non-SLNs harbored macrometastases, and 3.3% had micrometastases. When ALND was not performed, axillary recurrence was no seen. The reported low risk of non-SLN disease

in this setting provides further evidence in support of avoiding ALND for SLNs positive by IHC only.

On the contrary, according to Menes and Colleagues, who examined the nonsentinel nodes in 124 SLN-positive patients, nonsentinel node metastases were found in 19% of patients who had sentinel node metastases less than 0.2mm, 20% of patients who had SLN metastases measuring 02.mm to 2mm, and 46% of patients who had metastases greater than 2mm. This dataset demonstrates that in patients who are considered SLN-negative (metastases <.2mm) and in those who have micrometastases, omitting an axillary dissection may leave residual axillary disease in 20% of cases.

The discordant findings noted in these two studies provide further evidence that conclusive, prospective, long term data from multicenter trials evaluating issues specific to SLN biopsy is well awaited.

Survival impact

Other data to support avoiding ALND in SLN-positive patients comes from important clinical trails. During the 1970s, as part of the NSABP B-04 study, clinically node-negative patients were randomized to three treatment arms: radical mastectomy, total mastectomy with radiation, and total mastectomy with axillary observation. Regardless of the type of axillary management received (axillary lymph node dissection in the radical mastectomy group, radiation alone in the second group, or observation with delayed intervention in the third group), the overall survival was equivalence. This outcome equivalence has persisted on 25 years follow-up. These historical data from NSBP B-04 suggest that prophylactic resection of occult axillary metastases is comparable, in terms of survival, to axillary observation and delayed therapeutic ALND in cases of regional failure. NSABP B-04 suggests that ALND is unlikely to confer a survival benefit. Despite these findings, ALND has remained an essential component of breast cancer management

Accrual to this phase III clinical trial was completed in an era of surgical treatment alone for breast cancer management, before the advent of effective systemic therapy for breast cancer. Subsequently, axillary nodal status became the most powerful determinant of magnitude of benefit

from adjuvant systemic therapy. This remained true for several years while the adjuvant therapies for breast disease have continued to evolve. Decisions regarding additional therapy are now less dependent on the status of the axilla. Unfortunately, the B-04 study was not powered statistically to address the survival benefits of ALND; it was designed to evaluate the overall safety of modified surgical strategies (radical mastectomy versus total mastectomy versus total mastectomy and locoregional irradiation) as treatment for operable breast cancer. Thus critics continue to argue that locoregional control may provide some benefit in terms of survival.

Local recurrence:

When scrutinized further, NSABP B-04 data provide information regarding axillary recurrence. In the radical mastectomy group, 40% of the patients were found to have positive axillary lymph nodes, with the axillary recurrence rate approaching approximately 1%. Assuming equal randomization between the three treatment arms, one can deduce that approximately 40% of the patients in each group possessed axillary metastases. Within the group of patients treated with total mastectomy alone, without a specific axillary intervention, however, only 18.6% developed an axillary relapse as an initial treatment failure. As suggested by the NSABP B-04 study, clinically occult and untreated axillary metastases will progress into clinically evident disease requiring a delayed/therapeutic ALND in approximately half of cases, and this outcome does not appear to adversely affect survival when compared with patients whose axillary disease was detected by a staging ALND at the time of diagnosis.

Axillary recurrence after a level I or II axillary dissection is unusual, occurring in 0.5% to 3% of patients in the literature. More recently, several investigators have explored the rate of axillary recurrence after SLN biopsy. Since its introduction, the technique of SLN biopsy has evolved to optimize detection of axillary disease with false-negative rates approaching 5%. Given this, one might expect a rate of axillary relapse or distant recurrence greater than or equal to 5%. This is not the case, however, according to contemporary reports.

Jeruss and colleagues presented follow-up data on 864 patients. Of the 633 SLN-negative patients, 4.7% underwent completion ALND, while the remaining patients were observed. Only two (0.32%) SLN-negative patients developed recurrence within the axilla: one of which had undergone completion ALND. Sixty-eight percent of the SLN-positive patients were managed with ALND, while 32% were observed over a median follow-up of 27.4 months. There were no recurrences among the SLN-positive group. None of the study participants received radiation therapy with additional fields to include the axilla. They compiled 10 published reports of axillary relapse after sentinel node biopsy and calculated an overall recurrence rate of 0.4% suggesting that axillary observation may be a feasible alternative in cases of both negative and positive SLNs. Similarly, a pooled analysis by Smidt and colleagues evaluated over 3000 patients with a median follow-up of 25 months resulting in an axillary recurrence rate of 0.25% in SLN-negative patients. This included information from their own dataset, in which they encountered two patients who had axillary recurrence, representing 0.46% of the study population.

The Memorial Sloan Kettering group reported an overall rate of axillary recurrence of 0.25% after SLN biopsy. Only 10 axillary relapses were identified among all 4008 patients. Among 2340 SLN-negative patients treated without ALND, only three recurrences were seen, corresponding to a 0.12% axillary recurrence rate, providing further evidence that it is safe to omit ALND after a negative SLN. The local recurrence rates after positive SLN biopsy treated with and without ALND were 0.35% and 1.4%, respectively, in their opinion, the rarity of axillary recurrence after SLN biopsy confirms that SLN biopsy is at least equivalent to ALND in regards to staging the axilla and achieving local control of axillary disease.

Badgwell and colleagues at Ohio State University retrospectively reviewed patterns of recurrence after SLN biopsy in 222 patients with a minimum of 24-month follow-up. Of 159 SLN-negative patients, five (3%) developed recurrences. One had local (breast) recurrence, and four had distant recurrences. There were no isolated regional (axillary) recurrences within the SLN-negative

group. Among SLN-positive patients, the overall recurrence rate was 9.5%, with three local, one regional, and two distant recurrences. The complete absence of axillary relapse among the SLN-negative patients is comparable to an early prospective observational study by Giuliano and colleagues, in which no local, regional, or distant recurrences were noted among 67 SLN-negative patients, with a median follow-up of 39 months. After an extensive review if the literature, Newman reported upon 10 studies evaluating patients with negative SLNs treated without ALND. This report yielded results from 10 studies published between 2000 and 2005 in which the rate of axillary recurrence ranged from 0% to 1.4% over the course of 26 to 39 months.

Fewer studies have focused their evaluation on he rates of axillary and systemic failures after positive SLN biopsy. Published results from the John Wayne Cancer Institute in 2003 describe the outcome of 46 SLN-positive patients treated without completion ALND based on patient preference or increased operative risk. The degree of sentinel node disease ranged from cellular metastases in 50%, micrometastases in 35%, to macrometastases in the remaining 15% of study patients. After a mean follow-up of 32 months, zero axillary recurrences were identified, and one systemic recurrence was identified. Again, Newman reported the results of five separate studies evaluating the axillary recurrence rates among SLN-positive patients treated without SALND published between 2003 and 2005. The axillary recurrence rate ranged from 0% to 2.6% with average follow-up raging from 25 to 32 months.

Again, this is further evidence in favor of the SLN's ability to accurately stage the axilla. The results of several major clinical trials evaluating multiple long term outcome variables after SLN biopsy are anticipated however.

American College of surgeons Oncology Group Z0010 trial

The American College of surgeons Oncology Group Z0010 trial

was designed to evaluate the prevalence and significance of micrometastases within the sentinel node and bone marrow of T1 and T2 breast cancer patients, and determine the rate of regional recurrence in

patients with negative SLNs by hematoxylin and eosin staining. Between 1999 and 2003, over 5500 patients were enrolled. In this prospective, single-arm, observational study, clinically node-negative patients undergoing breast conservation therapy and SLN biopsy also were subjected to bilateral bone marrow biopsy. ALND was performed in cases of SLN failure. SLNs deemed negative by hematoxylin and eosin (H&E) were sent to a core laboratory for immunohistochemical evaluation along with bilateral bone marrow aspirates. Patients who had one or two positive SLNs were then eligible for randomization in ACOSOG Z0011. Completion ALND was required for patients who had three or more positive SLNs, and for patients with one to two positive SLNs who did not consent to ACOSOG Z0011. Postoperatively, these patient were to receive whole-breast radiation without additional fields to include the supraclavicular lymph nodes. Adjuvant systemic therapy was recommended for all patients with SLNs positive by H&E. Primary and secondary endpoints included overall survival, disease-free survival, and axillary recurrence. In addition to determining the prevalence and prognostic significance of micrometastases detected by IHC, investigators also hope to glean some evidence regarding the rate of axillary recurrence in patients whose nodes are negative by H&E staining.

The first available published data from this trial report the surgical complications associated with SLN biopsy in 5327 patients. SLN metastases were identified by H&E staining in 24% of the study populations. Patients who subsequently underwent ALND were excluded from the analysis. Early complications such as anaphylaxis (0.1%), brachial plexus injury (0.2%) wound infection (1%), hematoma (1.4%), and seroma (7.1%) were relatively uncommon and much lower than seen with traditional ALND. It was noted, however, that patients who had five or more SLNs removed experienced increased rates of wound infection and seroma when compared with patients with fewer SLNs removed. Lymphedema was defined as an increase of 2cm from the presurgical arm measurement when compared with the contralateral arm. Six-month follow-up data reported axillary paresthesia (8.6%), decreased upper extremity range of motion (3.8%),and lymphedema (6.9%).

Increasing age and body mass index (BMI) were associated with an increased incidence of lymphedema after SLN biopsy. Interestingly, postoperative adjuvant radiation therapy was not associated significantly with an increased risk of upper extremity lymphedema. In their report of the ACOSOG Z0010 data, Wilke and colleagues presented an extensive review of the literature regarding complications after SLN biopsy versus ALND. According to their analysis of all available data, the incidence of lymphedema after ALND ranges from 7% to 20% as opposed to the low incidence of lymphedema noted among the Z0010 patients.

American College of surgeons Oncology Group Z0011 trial

The American College of surgeons Oncology Group Z0011 trial was phase III clinical trial for clinically node-negative patients with T1 or T2 tumors treated with breast conservation therapy and found to be SLN positive. Eligible patients who had a maximum of two positive SLNs were randomized to either completion ALND or axillary observation. The objectives of this study included assessing for the possible survival impact of ALND and comparing the morbidity associated with SLN biopsy alone versus SLN biopsy with completion ALND. Unfortunately, after 5 ½ years, Z0011 was closed because of poor accrual rates. A total of 891 patients were enrolled instead of the desired 1900. Very few adverse events were reported in either group, requiring a substantial increase in the number of patients enrolled in the study.

According to an abstract presented at the 2006 meeting of the American Society of Clinical Oncology, 1003 patients from the Z0010 trial were eligible for randomization on Z0011. Of these, only 37% were entered in Z0011. Z0010 participants accounted for 42% of patients in Z0011. Sixteen percent of patients not randomized refused ALND. Sixty-nine percent of those not randomized had ALND. Sixty-seven percent of these had no additional positive nodes. Only 14% had more than four positive nodes. In the opinion of the authors, clinical bias in favor of the standard of care, completion ALND, likely played a role in the failure to accrue. Despite this, the data suggest that most patients were without additional nodal disease upon completion ALND. Long-term follow-up data are not yet

available.

The American College of Surgeons Oncology Group (ACOSOG) attempted to define the value of the ALND in node-positive breast cancer by comparing disease-free survival, overall survival, post surgical morbidity, and local control in sentinel node-positive patients randomize to axillary observation versus the standard completion axillary surgery. The inability to complete this important trial likely will strengthen interest in use of statistical models that can identify patients likely to harbor additional metastatic nodes following resection of at least one metastatic sentinel node [43, 44]. The goal of these prediction tools is to refine the selection of SLN-positive patients who require completion ALND.

Axillary Lymphatic Mapping Against Nodal Axillary Clearance Trial

The ALMANAC trial was a multicenter randomized study that compared postsurgical morbidities and quality-of-life outcomes associated with SLN biopsy versus ALND. Between 1999 and 2003, 1031 clinically node-negative breast cancer patients were randomized to SLN biopsy or standard axillary surgery. In 2003, the trial was terminated early after it became apparent that patients randomized to the SLN arm experienced far less post-surgical morbidity. Follow-up data are available at 1, 3, 6, and 12 months after surgery. Initial reports indicate that the rated of lymphedema and sensory deficit were higher in the ALND group at all time points ($P<.001$). Shoulder abduction and flexion were also worse in the ALND group during initial follow-up assessment. As mobility improved, these differences persisted at subsequent time points, but were no longer statistically significant. Other advantages associated with SLN biopsy included shorter hospital stay, less axillary drain usage, and faster return to normal activities of daily living ($P<.001$ for all three variables).

NSABP B-32

NSABP B-32 was a large multicenter randomized phase III Clinical trial comparing SLND with ALND. With the help over 230 surgeons at 75 participating institutions, over 5600 clinically node-negative patients were accrued over a 4.5-year period between May 1999 and February 2004. Eligible

patients with T1-T3 invasive cancer were randomized to SLN biopsy followed by ALND versus SLN biopsy with ALND only in cases with failed SLN identification or positive SLN. All Patients who had negative SLNs will have further nodal evaluation with immunohistochemistry at a central laboratory. The investigators hope to demonstrate that patients who have a histologically negative SLN with no further axillary surgery will have the same long-term outcomes, with less morbidity, and better functional outcomes than those patients who subsequently receive a completion ALND. Comparisons will be made in regards to survival, locoregional control, and postsurgical morbidity. It is also hoped that this study will provide insight as to whether there is prognostic value associated with completion ALND after a positive SLN biopsy. Other secondary goals include confirming the success rate and accuracy of the SLN procedure, evaluating the sensitivity and specificity of frozen section evaluation, and determining the significance of immunohistochemically detected metastases.

Preliminary data are available regarding technical results in over 5200 patients. Consistent with previous reports in the literature, the overall rate of SLN identification was 97%. Allergic reactions were rare (0.7%). Twenty-six percent of patients possessed positive SLNs, and similar to results from Z0011, in 61.5% of the SN-positive patients, no additional positive nodes were found on completion ALND. There was no significant difference in SLN identification rates between the two groups of patients. Further results from this trial are forthcoming.

Predicting the status of nonsentinel nodes

Given the uncertainties regarding the survival benefits associated with the completion ALND, a valid argument can be made that the critical issue is to identify the subset of high-risk SLN-positive who are likely to have metastases beyond the SLN node. As mentioned previously. Menes and colleagues [19] identified nonsentinel node metastases in 19% of patients with sentinel node metastases less than 0.2mm, 20% of patients with SLN metastases measuring 0.2. mm to
2 mm, 46% of patients with metastases greater than 2 mm, this dataset demonstrated that in patients who are considered SLN-negative (metastases less than 0.2 mm) and those with micrometastases,

omitting an axillary dissection may leave residual axllary disease in 20% of patients. So the logical question arises: Can we identify patients with positive SLNs who can avoid a completion ALND safely?

Van Zee and colleagues [43] therefore developed a nomogram that estimates the likelihood that an individual SLN-positive patient will have additional metastatic nodes in the completion ALND specimen. Degnim and colleagues [44] conducted a meta-analysis of studies involving SLN biopsy with concomitant ALND, and this pooled analysis provides a robust assessment of Clinicopathologic features associated with likelihood of detecting metastatic disease in nonsentinel nodes. Chu and colleagues [47] also evaluated clinicopathologic features of 157 patients who underwent SLN biopsy followed by ALND to determine risk factors for nonsentinel node involvement. All of these investigators have found primary tumor size and extent of SLN pathology to be strong predictors of non-SLN disease. Despite the fact that the nomogram does not offer treatment recommendations, it often is employed in clinical practice.

Viale and colleagues [48] examined the SLNs and non-SLNs of over 1200 patients in a similar fashion to also produce a predictive model. According to their data. The size and number of SLN metastases and lymphovascular invasion were significant predictors of further axillary involvement. In their opinion, even SLN-positive patients with the lowest possible predicted risk of additional disease (13%) should be offered completion axillary lymph node dissection. Similarly, other investigators have weighed in on this issue with concordant results. Katz and colleagues [49] conducted a retrospective evaluation of the records of ever 1133 patients undergoing SLN biopsy, which **on 367 SLN-positive patients. Increasing number of positive** SLNs, decreasing number of negative SLNs, increasing size the SLN metastasis, and the presence of lymphovascular invasion were associated with the likelihood of finding additional nodal diseases on completion ALND. The lowest calculated risk of additional disease in their study cohort was still 14%. Interestingly, according to their extensive review of literature, the rate of non-SLN metastases in patients with sentinel lymph node micrometastases

ranged from 0% to 34%. In this study, Katz and colleagues offered that they also recommend completion axillary lymph node dissection in the setting of a positive SLN until definitive clinical trail data stating the contrary are available.

Is there still a role for axillary lymph node dissection?

According to the available data, SLN biopsy is proving to be an accurate staging technique with less postsurgical morbidity than standard ALND. Survival benefits associated with SLN biopsy and ALND, and the significance of IHC-detected micrometastases have yet to be determined. The long-term results of several multicenter trials are pending, yet preliminary results are in favor of abandoning ALND in favor of the less-invasive alternative.

Despite this, ALND remains the standard of care in breast cancer patients who have clinically palpable axillary lymph nodes that are suspicious for metastatic disease. Although controversial, many clinicians believe that axillary metastases will precede systemic spread of disease. Therefore, axillary clearance of clinically palpable nodes could quell the progression of metastases. Regardless of whether this theory is true, not many would argue against debulking suspicious nodal disease.

ANATOMY OF THE BREAST

15 to 20 lobes of tubuloalveolar glandular tissue, fibrous connective tissue that supports it lobe, and the adipose tissue that resides in parenchyma between the lobes. Subcutaneous connective tissue typically does not form a distinctive capsule around breast components, nut, rather, surrounds the gland and extends as septa between the lobes and lobules, providing support to the glandular elements. The deep layer of the superficial facia that lies on the posterior surface of the breast fuses with the deep (pectroa) fasica of the chest wall. A distinct space, the retromammary bursa, can be identified anatomically on the posterior aspect of the breast and resides between the deep layer of the superficial facia and the deep investing fascia of the pectoralis major and the contiguous muscles of the thoracic wall. The retromammary bursa contributes to the mobility of the breast on the chest wall. Fibrous thickenings of supportive connective tissue interdigitate between the parenchymal tissue of the breast and extend from the deep layer of the superficial fascia to attach to the dermis of the skin. These suspensory structures, known as cooper's ligaments, insert perpendicular to the dermis,

SKIN

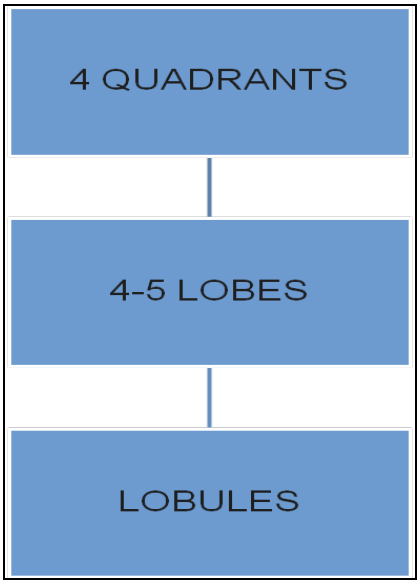
- ***THE AREOLA*** : Pigmented , sebaceous glands , Montgomery tubercles
- ***THE NIPPLE*** {papilla mammaria} :

No glands, circumferential muscle fibres , elastic tissue.

- Labia minora matches this skin.
- Lines of Langer

- Dynamic lines of kriasl

STRUCTURAL ANATOMY

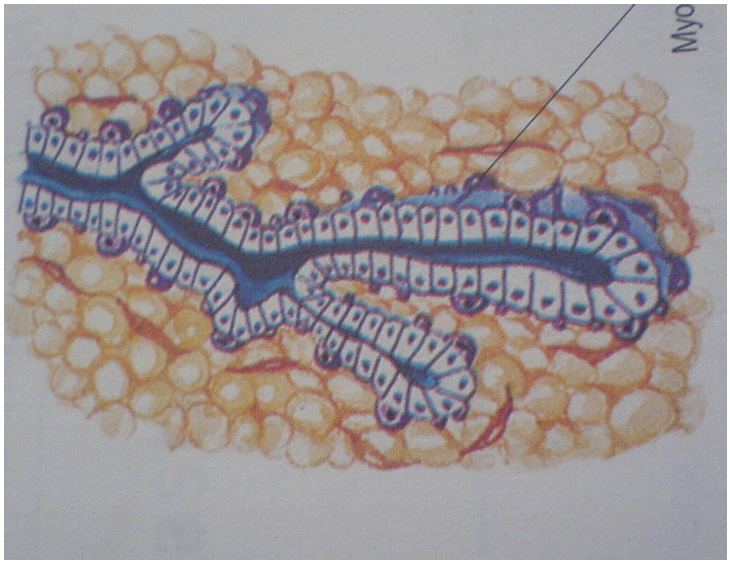


MICROSTRUCTURE

- **Tubulo alveolar glands**

- **Fibrous connective tissue stroma**

- **Interlobular adipose tissue**

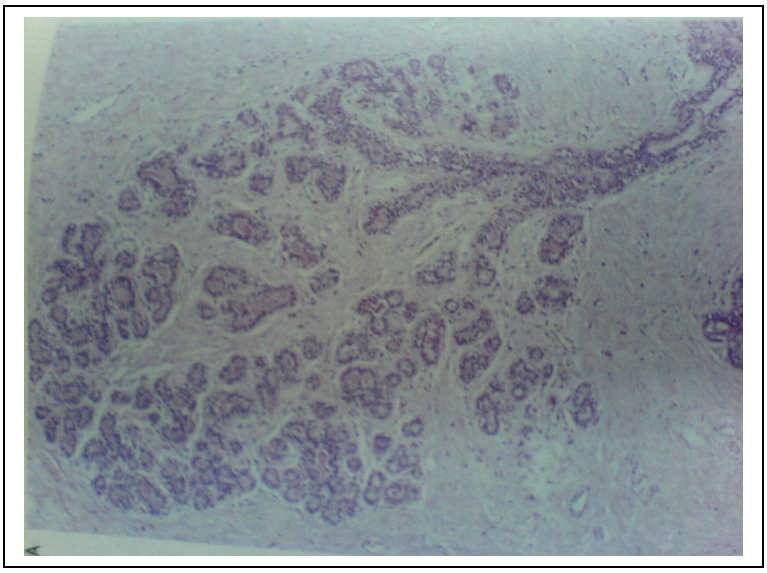


GROSS ANATOMY	HISTOLOGY	PATHOLOGY
Ducts	Two layers of columnar epithelium	Papilloma, Ectasia
Ductules	Single layer of cuboidal epithelium	Fibro adenoma, cysts sclerosing lesions
Terminal ductules	Cuboidal epithelium	Adeno carcinoma

STROMA

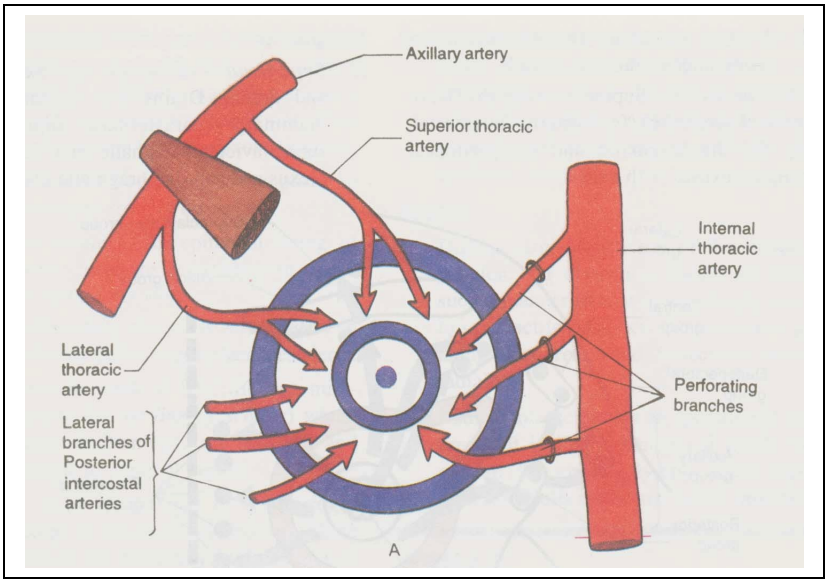
INTRALOBULAR STROMA- Connective tissue stroma loose texture allowing rapid expansion of secretory tissue during pregnancy

- INTERLOBULAR STROMA- suspensory ligaments {of Ashtley Cooper} condensations of fibrous tissue from ducts to dermis, more in the upper quadrants



ARTERIAL SUPPLY

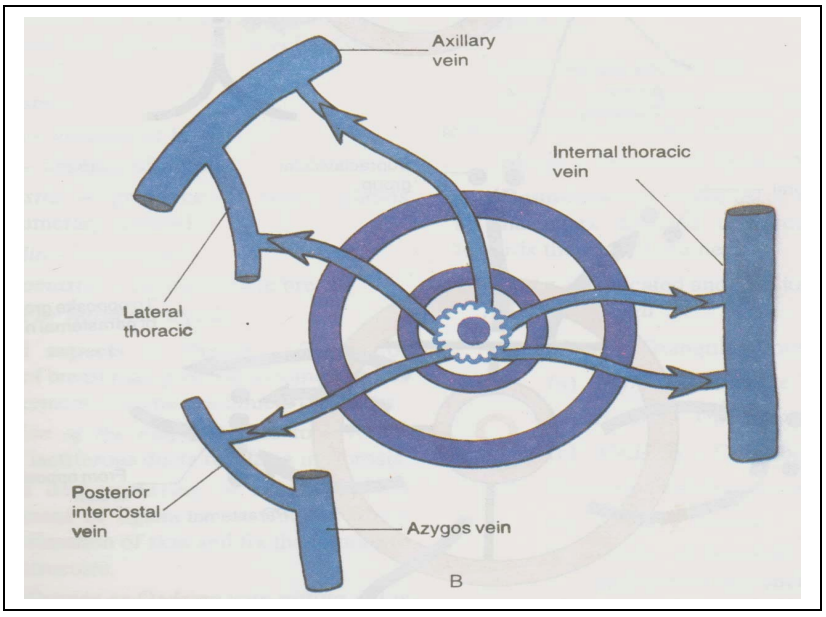
- Lateral thoracic branch of 2nd part of axillary artery
- Medial mammary branches of internal thoracic artery
- Superior thoracic branch of axillary artery
- Lateral branches of 2nd,3rd,4th posterior intercostal arteries



VENOUS DRAINAGE

- Circulus venosus - venous plexus deep to the areola
- From this plexus two sets of veins are formed :

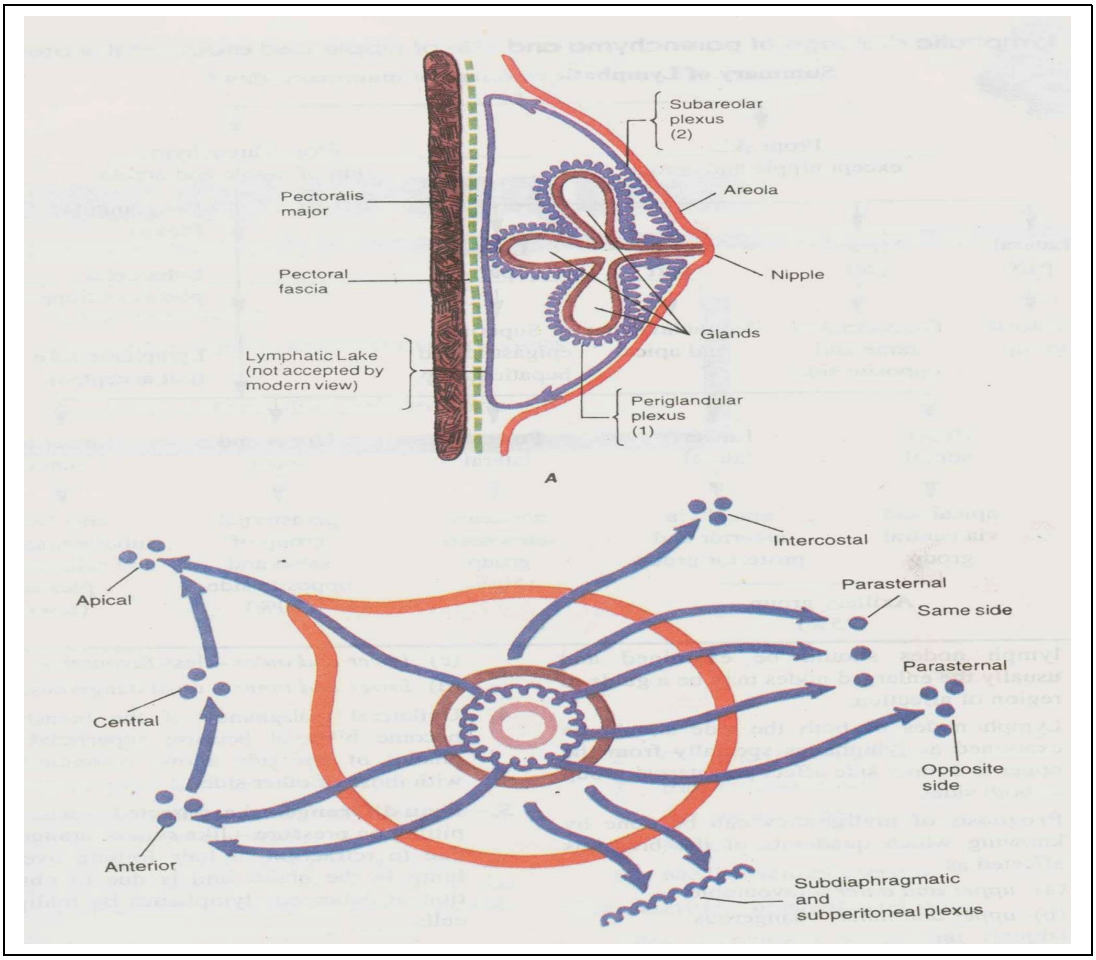
1. superficial set- ends in internal thoracic vein
2. deep set - ends in internal thoracic, axillary and post intercostal veins



LYMPHATIC DRAINAGE

- AXILLARY NODES- 75 % of lymph
- PARASTERNAL NODES- remaining lymph
- GROUPS – ANATOMISTS - 5 SURGEONS - 6

  - lateral or axillary vein group
  - external mammary or pectoral or medial group
  - scapular or posterior group
  - central group
  - subclavicular or apical group
  - interpectoral or rotter group



LEVEL 1 NODES:

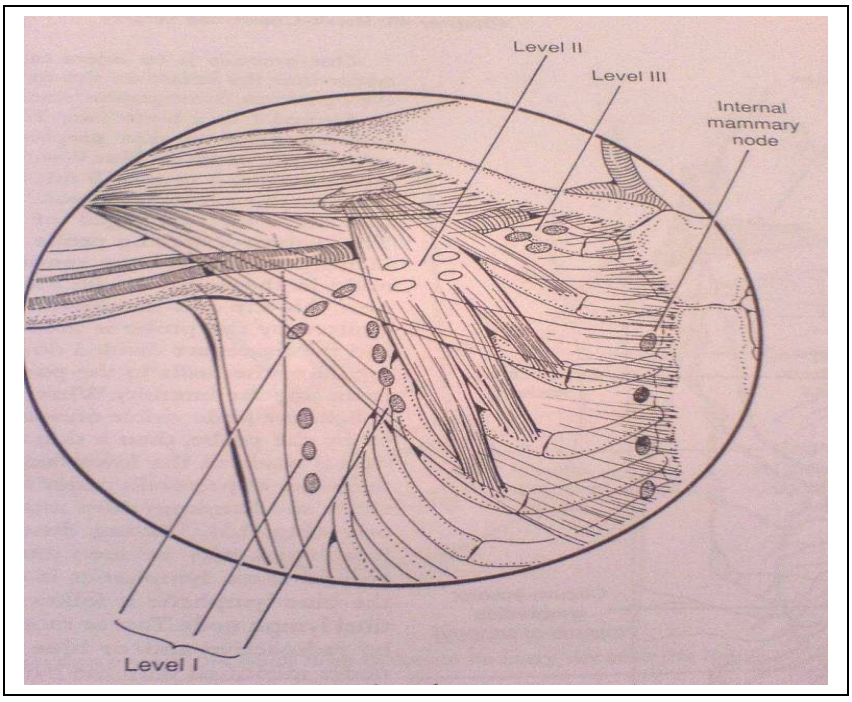
lateral to the lateral border of pectoralis minor muscle externalmammary,scapular axillary vein and central groups

LEVEL 2 NODES:

under the pectoralis minor muscle central, axillary group

LEVEL 3 NODES: BERG

subclavicular nodes medial border of pectoralis minor and first rib



ANATOMY OF AXILLARY TENT

- BASE- Axillary fascia
- APEX- aperture that extends into the posterior triangle of neck thro CERVICO AXILLARY CANAL
- ANTERIOR WALL – Pectoralis muscles and fascia

- POSTERIOR WALL- Subscapularis , Teresmajor, Lattismus Dorsi.
- LATERAL WALL- Bicipital groove
- MEDIAL WALL- Serratus anterior
- CLAVIPECTORAL FASCIA:
- upper portion –COSTOCOROCOID MEMBRANE pierced by

  cephalic vein lateral pectoral nerve, branches of thoraco acromial artery

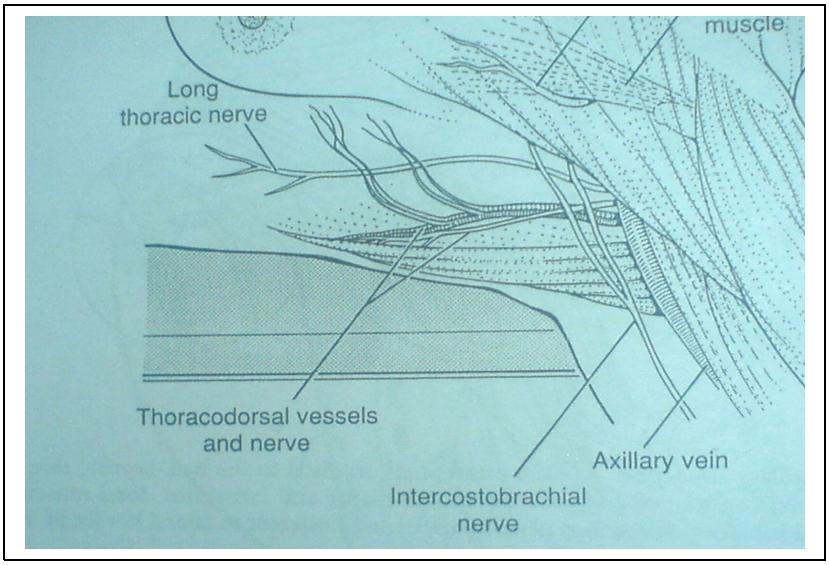
  Middle portion- pectoralis minor pierced by median pectoral nerve
- Lower portion –CORACO AXILLARY ligament HALSTEAD

  LIGAMENT- medial side of clavicle to the first rib
- AXILLARY ARTERY: 3 PORTIONS identification of the branches of 2nd portion is essential**.**

ANATOMICAL STRUCTURES OF IMPORTANCE

- THREE NERVES:
- LONG THORACIC NERVE- medial wall of axilla lies on the serratus anterior fascia . Division leads to winging of scapula
- THORACO DORSAL NERVE – origin from posterior cord supplies lattismus dorsi, preservation essential for TRANSFER SURVIVAL &MOTOR FUNCTION of MYOCUTANEOUS FLAP used for lattismus dorsi musculocutaneous reconstruction
- INTERCOSTO BRACHIAL NERVE- parasthesia of uppermedial and inner aspect of arm
- HALSTEAD LIGAMENT- upper limit of axillary dissection

- branches of 2nd portion of AXILLARY ARTERY – THORACO ACROMIAL & LATERAL THORACIC ARTERY .



STUDY SUBJECT:

Biopsy proven carcinoma breast patients admitted at Govt Rajaji Hospital during the period of 2006 to 2008 ,under surgical units 1 to 7 and surgical oncology department with tumour size less than 3 cms and clinically axillary node negative status

MAPPING AGENT USED : METHYLENE BLUE

Methylene blue dye was for its low side effects and cost benefit and easy availability

TECHNIQUE :

7ML of sterile methylene blue was injected 7 minutes before surgery peritumourmally and subdermally

PROCEDURE:

Under general anesthesia, axillary incision was made subdermal blue colored lymphatics were traced upto the first colored node (sentinel node).node was dissected out and sent for histopathological examination.

OBSERVATION & DISCUSSION OF THE STUDY

The study is a prospective study done in Govt Rajaji Hospital dept of surgery and surgical oncology in female patients of carcinoma breast of stage 1(T1NO). The surgery done was MRM along with sentinel node biopsy. The dye used was methylene blue.

The technique used was 7ml of the dye was injected seven minutes before surgery, peritumourally and subdermally. The patients were proceeded with MRM, first phase of the surgery axillary dissection was done and first coloured sentinel node was removed after that MRM continue along with other lymphnodes in the axilla were dissected. The first coloured sentinel node send separately for histopathological examination along with other axillary lymphnodes and breast tissue with the mass. No complications were recorded during the procedure or during the surgery.

Review of the histopathology examination of the sentinel node and other axillary nodes were indicative of 80% positivity of sentinel node sample along with other axillary nodes ,while fallacy was noted with negative SLNB and positive axillary nodes in the remainder of the patients.

Postoperatively patients were put on 6 cycles of chemotherapy and harmone therapy and followed upto 2years no local recurrence or systemic metastasis were recorded.

CONCLUSION

THE STUDY WAS SUCCESSFULLYCOMPLETED AND SHOWS ABOUT 80% POSITIVITY OF SLNB (sentinel node positive patients were also having positivity of the other axillary node while negative patients had negativity of other axillary nodes)

This is was a useful and cost effective study with no major complications and reliable technique for day to day practice and having the advantage of ruling out radical surgical procedures and major complications post operatively.

Summary

The value of SLNB in the staging and prognosis of breast cancer patients with early stage disease is defined clearly, and lymphatic mapping is becoming the standard of care for most centers. It is projected that SLNB will soon replace ALND completely as the initial evaluation procedure of the axillary nodal basin for metastases. As the specifics of lymphatic mapping evolve, the process should be individualized and tailored to institutional capabilities and the practice preferences of the entire multidisciplinary team to yield the most consistent and reliable results.

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PROFORMA

NAME : AGE : SEX :

INPATIENT NO :

UNIT :

DOA : DOS :

SIDE AND QUADRANT :

SIZE OF THE TUMOUR :

AXILLARY LYMPH NODE STATUS :

STAGE :

DYE USED FOR SLN MAPPING : METHYLENE BLUE

TIME OF INJECTION : 7 MINUTES BEFORE SURGERY

SITE OF INJECTION : 1)SUBDERMAL & PERITUMOURAL

SURGICAL TECHNIQUE : AXILLARY INCISION FIRST

FOLLOWED BY MRM

BIOPSY RESULTS :

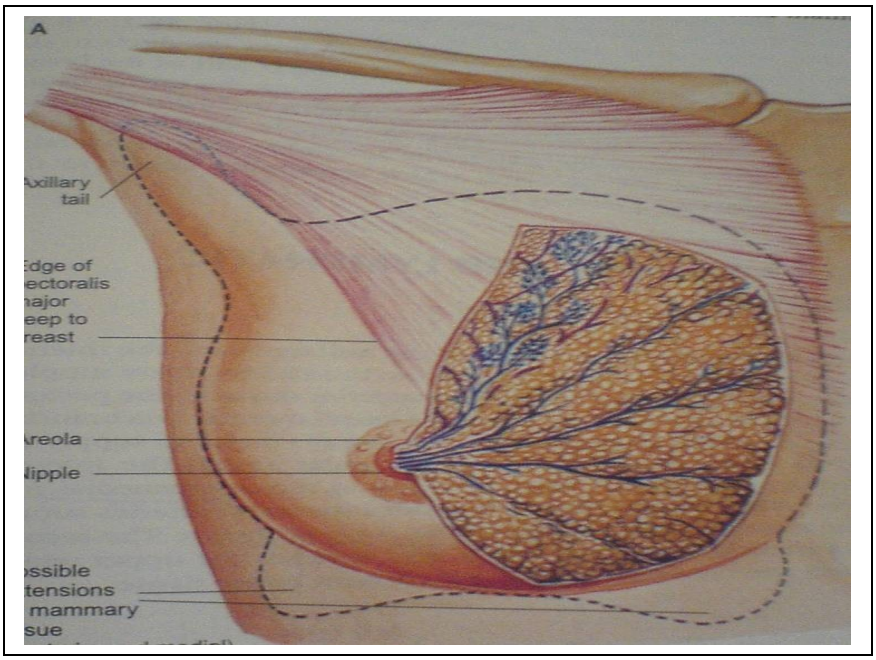
POST PROCEDURE MANAGEMENT:

FOLLOW UP :

OUTCOME OF THE STUDY :

CONCLUSION :

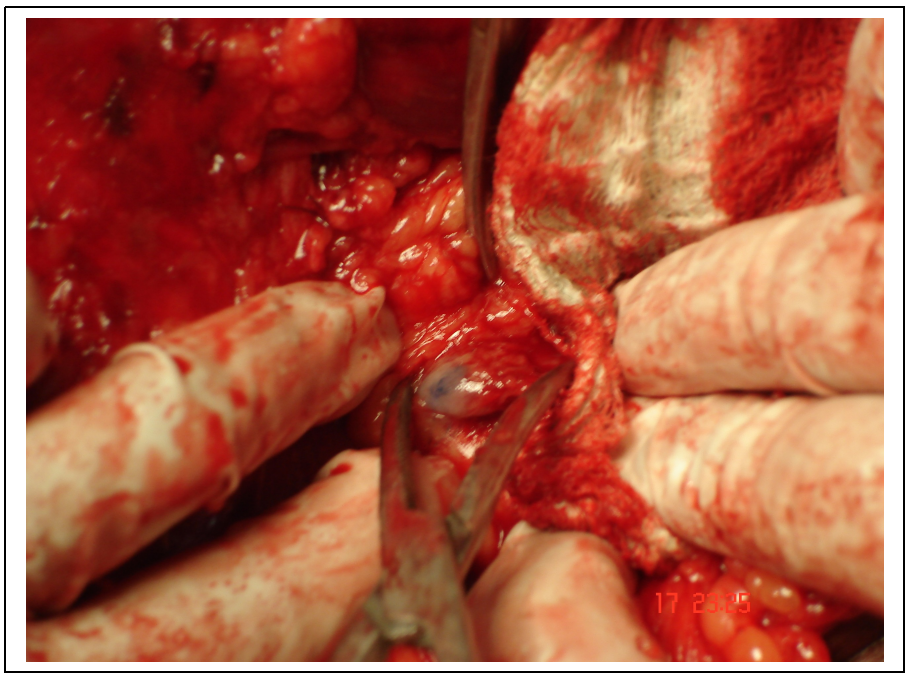
ANATOMY


A
Axillary tail
Edge of pectoralis major deep to breast
Areola
Nipple
possible extensions of mammary tissue

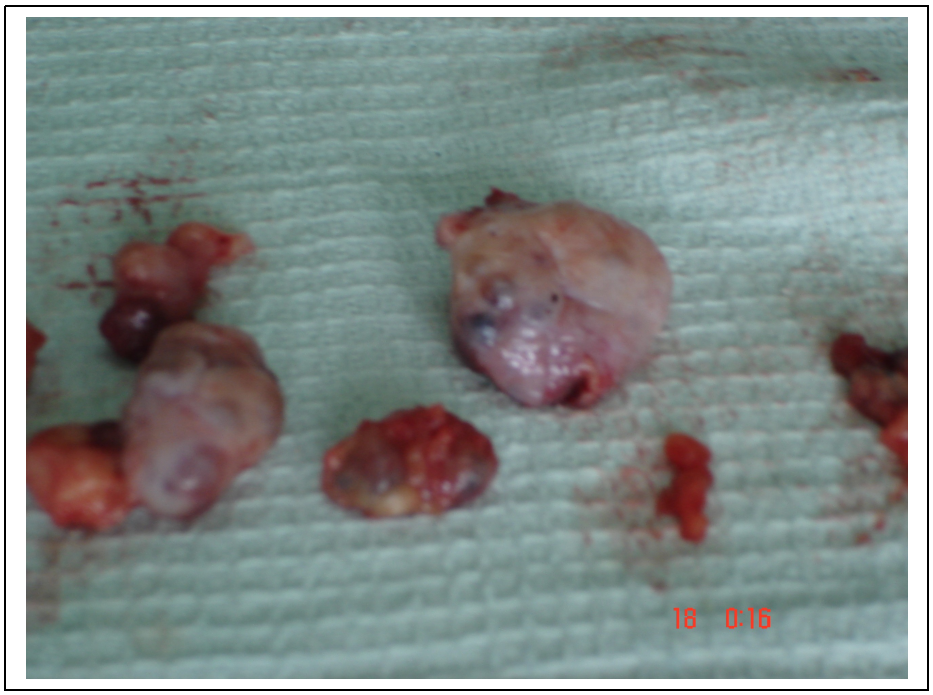

17 0:08

AXILLARY INCISION

FIRST COLOURED SENTINEL NODE



DISSECTED AXILLARY LYMPHNODES



MASTER CHART

S.No.	Name	Age	Sex	IP No.	Diagnosis		Sentinel node HPE report	Other axillary nod HPE
1)	VIJAYALAKSHMI	40	F	46229	CA BREAST RT	T1N0M0	Negative	Negative
2)	RAJATHI	42	F	562440	CA BREAST RT	T1N0M0	Negative	Negative
3)	LAKSHMI	40	F	761	CA BREAST LT	T2N0M0	Negative	Positive
4)	KALANJIYAM	40	F	1156	CA BREAST RT	T1N0M0	Positive	Positive
5)	MUTHULAKSHMI	41	F	8662	CA BREAST LT	T2N0M0	Negative	Negative
6)	VALLI	45	F	5170	CA BREASTRT	T1N0M0	Positive	Positive
7)	ANJAMMAL	36	F	1034	CA BREAST LT	T1N0M0	Negative	Negative
8)	CHITRA	30	F	11224	CA BREAST LT	T1N0M0	Negative	Negative
9)	RAJALAKSHMI	47	F	11237	CA BREAST LT	T1N0M0	Negative	Positive
10)	SUBBUTHAI	38	F	33283	CA BREAST RT	T1N0M0	Negative	Positive

11)	SUDHA	45	F	33286	CA BREAST LT	T1N0M0	Negative	Negative
12)	KAMALA	30	F	53302	CA BREAST LT	T2N0M0	Negative	Negative
13)	PICTHAMMAL	35	F	34778	CA BREAST RT	T1N0M0	Negative	Negative
14)	MANIMEGALAI	43	F	35638	CA BREAST LT	T2N0M0	Positive	Positive
15)	JOTHIAMMAL	45	F	37082	CA BREAST RT	T1N0M0	Negative	Negative
16)	MAHALAKSHMI	48	F	38615	CA BREAST LT	T1N0M0	Negative	Positive
17)	BAMA	35	F	40703	CA BREAST LT	T1N0M0	Negative	Negative
18)	CHELLAIAMMAL	43	F	41797	CA BREAST RT	T1N0M0	Negative	Negative
19)	PARAMESHWARI	43	F	100383	CA BREAST LT	T1N0M0	Negative	Negative
20)	MALAIYKAL	40	F	94716	CA BREAST RT	T1N0M0	Negative	Negative
21)	GOMATHI	39	F	88775	CA BREAST LT	T1N0M0	Positive	Positive
22)	EASWARI	45	F	47896	CA BREAST LT	T1N0M0	Negative	Positive
23)	VALLI	45	F	52391	CA BREAST RT	T1N0M0	Negative	Negative
24)	Selvi	35	F	63450	CA BREAST LT	T1N0M0	Negative	Negative
25)	Fathima	60	F	6889	CA BREAST RT	T1N0M0	Negative	Negative
26)	Rajammal	60	F	69643	CA BREAST LT	T2N0M0	Negative	Positive
27)	Gomathi	45	F	52133	CA BREAST RT	T1N0M0	Positive	Positive
28)	Banu	42	F	53134	CA BREAST LT	T1N0M0	Negative	Negative
29)	Gandhimathi	40	F	52444	CA BREAST RT	T1N0M0	Negative	Negative
30)	Krishnammal	39	F	53265	CA BREAST RT	T1N0M0	Positive	Positive